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2015 European Society of Coloproctology collaborating group; Qvist, Niels

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## **The relationship between method of anastomosis and anastomotic failure after right hemicolectomy and ileo-caecal resection: an international snapshot audit**

On behalf of the 2015 European Society of Coloproctology collaborating group\*

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## Abstract

**Background:** Anastomosis technique following right sided colonic resection is widely variable and may affect patient outcomes. This study aimed to assess the association between leak and anastomosis technique (stapled versus handsewn) .

**Methods:** This was a prospective, multicentre, international audit including patients undergoing elective or emergency right hemicolectomy or ileo-caecal resection operations over a two-month period in early 2015. The primary outcome measure was the presence of anastomotic leak within 30 days of surgery, using a pre-specified definition. Mixed effects logistic regression models were used to assess the association between leak and anastomosis method, adjusting for patient, disease and operative cofactors, with centre included as a random effect variable.

**Results:** This study included 3208 patients, of whom 78.4% (n=2515) underwent surgery for malignancy and 11.7% (n=375) for Crohn's disease. An anastomosis was performed in 94.8% (n=3041) of patients, which was handsewn in 38.9% (n=1183) and stapled in 61.1% (n=1858) cases. Patients undergoing handsewn anastomosis were more likely to be emergency admissions (20.5% handsewn versus 12.9% stapled) and to undergo open surgery (54.7% versus 36.6%). The overall anastomotic leak rate was 8.1% (245/3041), which was similar following handsewn (7.4%) and stapled (8.5%) techniques (p=0.3). After adjustment for cofactors, the odds of a leak were higher for stapled anastomosis (adjusted odds ratio 1.43, 95% confidence interval 1.04-1.95, p=0.03).

**Discussion:** Despite being used in lower risk patients, stapled anastomosis was associated with an increased anastomotic leak rate in this observational study. Further research is needed to define patient groups in whom a stapled anastomosis is safe.

## Introduction

Morbidity following colorectal resection is common. Up to 65.3% of patients suffer a complication in the first 30 days after surgery, which is major in 17.1% (Clavien-Dindo grade III-V) <sup>1</sup>. These complications impact upon both morbidity and mortality rates, as well as increasing healthcare costs<sup>2-4</sup>. Anastomotic leak is considered as one of the most devastating of these adverse events, and is associated with a reduction in both survival and quality of life, and an increased risk of disease recurrence in those patients with cancer<sup>2</sup>.

Many factors are known to be associated with anastomotic leak including patient comorbidity, underlying pathology and anastomotic technique. There is a wide variation in the use of handsewn versus stapled anastomosis, illustrating the lack of high quality evidence supporting either method<sup>5</sup>. More evidence is required to guide surgical practice. Right hemicolectomy (including ileo-caecal resection) is the most common colonic resection, is performed in both elective and emergency settings, and for neoplastic and non-neoplastic conditions. It therefore represents an appropriate patient cohort in which to assess the relationship between method of anastomosis method and outcome.

Multicentre snapshot audits have the ability to gather large patient numbers in short periods of time from many hospitals. They provide contemporaneous and population based data that is representative of current practice, and which is unconstrained by the confines often required in clinical trials. This first report from an international prospective cross-sectional cohort study of right hemicolectomy and ileocaecal resections investigates the relationship between anastomosis method and subsequent anastomotic leak.

## Methods

This prospective, observational, multicentre study was performed according to a pre-specified protocol (<http://www.escp.eu.com/research/cohort-studies/2015-audit>). The protocol and data entry system were tested and modified following an external pilot conducted in eight centres across five countries prior to the start of the main project. Follow-up and data collected was restricted to routinely collected data fields.

### *Centres*

Any unit performing gastrointestinal surgery was eligible to register and enter patients into the study. No unit size or case volume stipulations were made and centres from any country were able to take part. The study was launched at the European Society of Coloproctology (ESCP) Scientific & Annual Meeting in Barcelona, September 2014 and invitations to participate were subsequently distributed directly to all registered members of the ESCP. Further dissemination was obtained via the national ESCP country representatives, including through national surgical or colorectal societies. In addition, the study was endorsed and disseminated by the surgical arm of the European Crohn's and Colitis Organisation.

### *Approvals*

Participating centres were responsible for completion of local approvals prior to the start of the data collection period. Regional or national ethics approval or indemnity was obtained where possible. Centres were asked to ensure that appropriate pathways and local investigators were in place to be able to include all consecutive eligible patients during the study period and provide >95% completeness of data entry.

## *Patients*

Adult patients undergoing right hemicolectomy or ileo-caecal resection for any pathological indication, via any operative approach in both the elective and emergency settings were included. Patients were excluded if their right sided colonic resection was as part of a larger procedure (e.g. subtotal colectomy or panproctocolectomy), as defined by a distal colonic transection point beyond the splenic flexure. In patients with Crohn's disease, those undergoing additional proximal strictureoplasty or resection/anastomosis of more proximal small bowel disease during the same operation were also excluded.

## *Outcome measures*

The primary outcome for this study was overall anastomotic leak, pre-defined as either i) gross anastomotic leakage proven radiologically or clinically and classified according to intervention necessary (figure 1), or ii) the presence of an intraperitoneal (abdominal or pelvic) fluid collection on post-operative imaging. Secondary outcome measures included mortality, overall morbidity and length of hospital stay. An exploratory sensitivity analysis was also undertaken of those with only a 'proven' anastomotic leak (i.e. excluding those with an intraperitoneal fluid collection alone) for comparison purposes.

## *Data collection*

Sites were asked to include all consecutive eligible patients over an eight week period, which could start at any time between the 15<sup>th</sup> and 30<sup>th</sup> January 2015. This flexible starting date was designed to maximise centre participation. The final date for any new patient inclusions at any site was March 27<sup>th</sup> 2015.

There were three main phases of data collection for each patient:

- |                  |  |
|------------------|--|
| a) Pre-operative | patient (e.g. age, gender, co-morbidities) and disease demographics (e.g. indication, previous treatment)                                    |
| b) Operative     | technical details about the operation performed (e.g. handsewn or stapled anastomosis; laparoscopic or open approach; elective or emergency) |
| c) Follow-up     | individual outcomes data (anastomotic leak, length of hospital stay, mortality); completed at 30 days post-operation.                        |

Each of these phases had a separate clinical reporting form (CRF) that contained 10-12 main questions and was designed to fit in with data collected as part of normal clinical practice and be completed in 'real-time' with minimal extra work from the clinical team.

Despite no changes being made to existing patients' pathways during this observational study, local investigators were asked to be proactive in identifying postoperative events.

Methods included review of patient notes (paper and electronic) during admission and before discharge, reviewing hospital systems to check for re-attendances or re-admissions, and reviewing postoperative radiology reports. Some centres routinely reviewed patients 30 days after surgery or used a telephone review, both of which were used to identify adverse events. Data was recorded contemporaneously and stored on a dedicated, secure, web-based platform without using patient identifiable information. Data was collected by a team of 4-5 people at each site, one of whom had to be a consultant surgeon who was responsible for the data quality at that centre.

### *Statistical analysis*

This report has been prepared in accordance to guidelines set by the STROBE (strengthening the reporting of observational studies in epidemiology) statement for observational studies<sup>6</sup>.

The primary aim of this study was to assess the association between the primary outcome measure (overall anastomotic leak) and the main explanatory variable of interest, anastomosis method (handsewn versus stapled anastomosis). Univariate and multivariate mixed effects logistic regression models (with centre included as a random effect) were fitted for overall anastomotic leak and the pre-specified explanatory variables: anastomosis method (handsewn or stapled), age, gender (male or female), body mass index (normal, underweight, overweight or obese), smoking status (never, ex-smoker, current or not known), history of ischaemic heart disease or cerebrovascular disease (no or yes), history of diabetes (none, diet/tablet controlled or insulin controlled), indication for operation (malignancy, Crohn's disease or other), American Society of Anaesthesiologists (ASA) grade (low or high risk), surgery type (elective or emergency), operation type (laparoscopic or open) and extent of surgery (complete, extended or limited; figure 2). These factors were chosen based on clinical significance and were all pre-specified in the statistical analysis plan. All the explanatory variables were included in the multivariate model irrespective of statistical significance in the univariate model, as this allowed potential confounding factors relating to the patient, disease and operation to be taken into consideration in the multivariate model.

Effect estimates are presented as odds ratios (OR) with 95% confidence intervals (95% CI) and two-sided p-values. An  $OR > 1$  indicated increased likelihood of anastomotic leak with the relevant explanatory variable compared to the reference category for that variable. Statistical significance was defined at the level of  $P < 0.05$ . Data analysis was undertaken using Stata version 14.



Sensitivity analyses were undertaken which included (1) fitting a multivariate model including anastomosis method and only those explanatory variables where  $p \leq 0.1$  in the univariate analysis; (2) fitting a multivariate model including only those explanatory variables where  $p \leq 0.1$  in the univariate analysis; and (3) fitting a multivariate model as per the primary analysis, but only including those patients with a 'proven' anastomotic leak in the outcome variable.

## Results

### *Data completeness*

Overall 97.4% of records had all data fields completed. Patient demographic details, basic operation details and 30-day outcome data were mandatory fields for records to be locked and as such had a 100% completion rate. The small levels of missing data predominantly related to patient smoking status and pre-operative medical therapy (in the case of Crohn's disease patients) subsections.

### *Patients and centres*

This study included 3208 patients from 284 centres in 39 countries (figure 3). There were five participating centres outside of Europe. The mean age of patients was 66 years (range: 16-99), 50.8% were male, the majority were never-smokers (62%), did not have history of ischaemic heart disease or cerebrovascular disease (80.5%) and were not diabetic (84.4%) (table 1). Most patients underwent surgery for malignancy (78.4%;  $n=2515$ ) or Crohn's disease (11.7%;  $n=375$ ). Overall, 81.3% ( $n=2609$ ) of patients underwent elective surgery, and 54.6% ( $n=1751$ ) of operations were started laparoscopically; 9.6% undergoing subsequent conversion to open. Further demographic details are shown in table 1.

### *Anastomosis technique*

An anastomosis was performed in 94.8% (n=3041) of patients, which was handsewn in 38.9% (n=1183) and stapled in 61.1% (n=1858) cases (table 1). There was no difference in stapled anastomosis rates in those undergoing surgery for malignancy (59.8%) and for Crohn's disease (58.7%). Patients undergoing handsewn anastomosis were more likely to be emergency admissions (20.5% versus 12.9% stapled) and to undergo open surgery (54.7% versus 36.6%).

### *Incidence of Anastomotic Leak*

The primary outcome measure of anastomotic leak and/or intraperitoneal fluid collection was present in 8.1% (245/3041) (table 2).

### *Univariate Analysis of Anastomotic Leak*

The mixed effects logistic regression analysis included 3013 patients and 242 leaks (there were 28 patients (0.9%) with missing data on extent of surgery who were excluded from this analysis). There was no evidence of an association between leak and anastomosis method (stapled vs. handsewn: OR 1.16, 95% CI 0.86-1.57, p=0.3) (table 3). Female gender was significantly associated with a reduced risk of leak (OR 0.70, 95% CI 0.53-0.92, p=0.011), whilst being a current smoker (vs. never-smoker: OR 1.68, 95% CI 1.15-2.43, p=0.007), other indication for surgery (vs. malignant: OR=2.39, 95% CI 1.62-3.54, p<0.001), emergency surgery (vs. elective: OR 2.33, 95% CI 1.70-3.19, p<0.001), and open incision (vs. laparoscopic: OR=2.32, 95% CI 1.74-3.08, p<0.001) were all associated with an increased risk of leak (table 3). Weaker associations were found with age (OR 0.99, 95% CI

0.98-1.00,  $p=0.06$ ) and higher ASA grade (vs. low grade: OR=1.30, 95% CI 0.98-1.72,  $p=0.07$ ).

### *Multivariate Analysis of Anastomotic Leak*

When a multivariate mixed effects logistic regression model was fitted including all the pre-specified variables, a significant association was found between leak and stapled anastomosis (vs. handsewn: OR 1.43, 95% CI 1.04-1.95,  $p=0.03$ ). Other variables found to be significant under multivariate analysis were age (OR 0.99, 95% CI 0.98-1.00,  $p=0.04$ ), other indication for surgery (vs. malignant: OR=1.73, 95% CI 1.05-2.85,  $p=0.03$ ) and open incision (vs. laparoscopic OR=2.09, 95% CI 1.53-2.87,  $p<0.001$ ). Similar results were seen when the multivariate models were restricted to only those variables where  $p\leq 0.1$  in the univariate analysis, with anastomosis method included and excluded as a co-factor. Another sensitivity analysis including only those patients with a 'proven' anastomotic leak (150/3041; 4.9%) also gave similar results (Supplementary tables).

### *Secondary Outcomes*

The overall 30-day death rate was 3.2% (103/3208) (table 4); for those undergoing elective operations this reduced to 1.5% (38/2609). The median length of hospital stay was 7 days (range: 1-30+ days), and the 30-day re-operation and re-admission rates were 6.6% and 5.7% respectively. In those patients undergoing anastomosis who had an anastomotic leak and/or intraperitoneal fluid collection, the 30-day death rate increased to 9.8%, and the length of hospital stay was more than doubled to a median of 18 days (table 4). When assessing only those patients with a 'proven' anastomotic leak, similar outcomes were seen; 30-day death rate, 11.3% and length of hospital stay, median 21 days (table 4).

## Discussion

This multicentre international snapshot audit has identified a possible association between stapled anastomosis and anastomotic leak. This became apparent following multivariate analysis that adjusted for other patient and disease characteristics, and operative information (with centre included as a random effect). This finding was perhaps surprising given that stapling was used more frequently in the lower risk groups, such as in elective and laparoscopic operations.

Multivariate analysis also found an association between operative approach and leak, with a greater risk of leak with open operations. This increased risk associated with open surgery was readily identifiable in both the emergency and elective settings and might be interpreted as suggesting that in modern surgical practice, the need for an operation to be undertaken using an open approach may be a surrogate marker of operative difficulty.

The association between anastomotic leakage and stapling only became apparent following multivariate analysis. There was a strong association between high risk patients and handsewn anastomosis which may have influenced our results. It is impossible to assign causation to this association, but it is interesting to speculate on the possible explanations: the effects of operative approach (open versus laparoscopic), operation urgency (elective versus emergency) and anastomosis method (stapled versus handsewn) are all likely to have contributed to this effect. This situation, where findings are non-significant in univariate but significant in multivariate analysis is well recognised in observational studies. Lo and colleagues identified various scenarios in which this situation may occur; one of which was indeed the presence of hidden interactions<sup>7</sup>.

### *Strengths of this study*

The prospective nature of data collection, using a standardised protocol and predesigned reporting system, ensured the quality and homogeneity of data returns. The wide variety of

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surgeons, sites and countries entering patients into this study increases the generalisability of the findings. Of the 39 countries involved, 34 were based in one continent (Europe), with other countries being spread across the world: Argentina, Brazil, China, Japan and USA. Bringing such a group together and coordinating over 1000 local researchers from 284 different centres to simultaneously collect uniform data and form a research network in this manner has been one of the most important successes of this first ESCP project. The number of sites involved, and patients entered, far exceeded our expectations when designing this project. Now the model has been shown to work, it is currently being used to undertake another prospective international audit<sup>8</sup> and the research network will also be perfectly poised to deliver future prospective interventional studies based on the areas of uncertainty identified in these audits.

### *Limitations*

Selection bias will always be an issue in this type of observational research. We have attempted to minimise the effects of this by undertaking adjusted analyses using mixed effects logistic regression models, but we accept that this can never fully counteract the nuances involved in clinical decision-making. Nonetheless, one might have predicted that any major selection bias effect on the primary outcome would favour stapling being actually at a diminished risk, given the prevalence of its use within the lower risk groups.

Reporting bias is also difficult to control for in this kind of study, where sites might have omitted uploading data for certain eligible patients within the study time period, either accidentally or deliberately, and the impact this could have on the results. We feel that this is unlikely given our study design, where the first two phases of data collection were prospectively and contemporaneously uploaded onto the online system in the pre-operative and immediate post-operative setting. This effectively 'locked' these patients into the audit and there was no case at any site where the follow-up data form was not completed for a

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patient whose data had been already entered into the first sections. Further, our results showing a high overall anastomotic leak rate, an overall 30-day death rate of 3.2%, and an elective 30-day death rate of 1.5% would suggest that patients with poor early post-operative outcomes have not been omitted.

It is possible that some patients included in the study may have undergone additional procedures such as simultaneous liver resection or extended resection due to pathological involvement of other local organs, as these were not pre-specified exclusion criteria. The numbers of such patients are likely to be very small and as such are unlikely to have conferred any major impact upon the main findings.

A potentially contentious decision was our inclusion of intra-abdominal and pelvic collections in with the 'proven' anastomotic leak group in our primary outcome definition. There is a lack of validated scoring system for anastomotic leak<sup>9-11</sup> and intraperitoneal fluid collections are considered by many surgeons as representative of an anastomotic leak until proven otherwise. One recent study confirmed that isolated free intraperitoneal fluid was not a benign finding after anterior resection and another showed that many patients with ultimately proven anastomotic leakage did not have classical peri-anastomotic signs or extravasation of contrast on imaging<sup>12,13</sup>. It is our opinion that inclusion of patients with an intraperitoneal collection within the primary outcome group of anastomotic leak was justified given the similarities in adverse outcome rates between this group and others with a confirmed leak. Similarly, the sensitivity analysis that included only the confirmed leak patients produced very similar results to those found in the main analysis. We consider therefore that the majority of patients with isolated intraperitoneal collections had sustained an occult anastomotic leak.

### *Comparison with the literature*

The anastomotic leak rate in this study compares closely with two other large-scale national audits utilising prospective data collection. The Spanish ANACO group recently identified an overall leak rate of 8.4% in 1102 patients undergoing elective right hemicolectomy for cancer<sup>5</sup> and a Dutch analysis of 15,667 patients undergoing anastomosis after colorectal cancer resection found anastomotic leak rates in the right hemicolectomy (n=7788) and ileocaecal resection (n=240) subgroups of 6.4% and 7.5% respectively<sup>14</sup>.

Our identification of stapling as a possible risk factor for anastomotic leak is contrary to a Cochrane review on the same topic<sup>15</sup>. This pooled data from 1125 patients undergoing an ileo-colic anastomosis within seven randomised trials and found fewer leaks after stapled anastomosis (2.5%; 11/441) compared to handsewn (6.1%; 42/684), which was statistically significant: OR 0.48 [0.24, 0.95] p=0.03. The authors rightly commented on the small patient numbers and the very low event rate. Whilst an apparently significant difference was found in leak rates, this did not correspond to a parallel impact upon re-operation rate, length of stay or mortality. Nevertheless this review concluded that “stapled anastomoses are associated with fewer anastomotic leaks than handsewn, and should be considered the standard against which all other techniques should be compared”. It is likely that surgeons may have changed their practice based on the conclusions from this highly respected data source. Our conflicting message on stapled anastomoses could perhaps be written off as statistical anomaly, were it not for the very same finding being identified in the recent Spanish ANACO multicentre study<sup>5</sup>. This prospective observational study from 52 centres found major anastomotic leak (requiring intervention) rates of 3.4% in handsewn and 7.8% in stapled anastomoses (OR 2.1 [1.1 - 4.2]; p = 0.007). Together with the current study, and accepting the potential shortfalls of observational research, this suggests that a more detailed investigation of stapled versus handsewn anastomosis is certainly warranted.

*Further research and analyses ongoing*

We recognise that another limitation of this study relates to the fact that there are many different stapling techniques used in anastomosis and grouping them together may be inappropriate. These include bowel orientation (side-side, side-end, end-side), the type of stapler used (linear, circular), the stapler used for apical transection (linear cutting, linear non-cutting) as well as other associated technical factors such as the use of staple line oversewing and staple height selection. Similar but less numerous variabilities also exist within the handsewn group. These technical details were all collected prospectively during the project but will be analysed and reported in a subsequent paper. It is possible that certain technical aspects, might account for a disproportionate number of leaks or make up the apparent difference in leak rates compared to the handsewn patients. Other subsequent reports from the study will explore the geographic variability in patients and techniques, and the impact of unit characteristics on outcome, and a detailed analysis of the perioperative management of Crohn's Disease patients against outcome is planned.

Despite being used in seemingly lower risk patients, stapled anastomosis was associated with increased anastomotic leak in this observational study. These findings indicate the need for further high quality, prospective and targeted research. It is likely that an updated large scale randomised trial of anastomotic technique in patients undergoing right sided bowel resection is needed.



Table 1: Patient, disease and operative characteristics by anastomosis type

Variable		Handsewn (N=1183)	Stapled (N=1858)	No Anastomosis (N=167)	Total (N=3208)
Patients Characteristics					
Age	Mean [SD]	66.4 [16]	66.1 [15.8]	63.4 [18.6]	66 [16.1]
	Median [IQR]	70 [59-78]	69 [59-77]	68 [54-77]	69 [59-77]
	Min - Max	16 - 97	16 - 99	20 - 94	16 - 99
Gender	Male	605 (51.1%)	935 (50.3%)	89 (53.3%)	1629 (50.8%)
	Female	578 (48.9%)	923 (49.7%)	78 (46.7%)	1579 (49.2%)
Body Mass Index	Normal	439 (37.1%)	671 (36.1%)	71 (42.5%)	1181 (36.8%)
	Underweight	39 (3.3%)	60 (3.2%)	8 (4.8%)	107 (3.3%)
	Overweight	384 (32.5%)	631 (34%)	39 (23.4%)	1054 (32.9%)
	Obese	321 (27.1%)	496 (26.7%)	49 (29.3%)	866 (27.0%)
Smoking Status	Never	754 (63.7%)	1141 (61.4%)	94 (56.3%)	1989 (62.0%)
	Ex-smoker	204 (17.2%)	354 (19.1%)	28 (16.8%)	586 (18.3%)
	Current	160 (13.5%)	224 (12.1%)	24 (14.4%)	408 (12.7%)
	Not known	65 (5.5%)	139 (7.5%)	21 (12.6%)	225 (7.0%)
History of Ischaemic heart disease or cerebrovascular disease*	No	918 (77.6%)	1532 (82.5%)	134 (80.2%)	2584 (80.5%)
	Yes	265 (22.4%)	326 (17.5%)	33 (19.8%)	624 (19.5%)
History of Diabetes	None	1000 (84.5%)	1564 (84.2%)	142 (85%)	2706 (84.4%)
	Diet/Tablet controlled	141 (11.9%)	239 (12.9%)	18 (10.8%)	398 (12.4%)
	Insulin controlled	42 (3.6%)	55 (3%)	7 (4.2%)	104 (3.2%)
Disease Characteristics					
Indication	Malignant	939 (79.4%)	1503 (80.9%)	73 (43.7%)	2515 (78.4%)
	Crohn's disease	123 (10.4%)	220 (11.8%)	32 (19.2%)	375 (11.7%)
	Other**	121 (10.2%)	135 (7.3%)	62 (37.1%)	318 (9.9%)
ASA Grade	Low risk	697 (58.9%)	1250 (67.3%)	60 (35.9%)	2007 (62.6%)
	High risk	486 (41.1%)	608 (32.7%)	107 (64.1%)	1201 (37.4%)
Operative Information					
Surgery type	Elective	941 (79.5%)	1618 (87.1%)	50 (29.9%)	2609 (81.3%)
	Emergency	242 (20.5%)	240 (12.9%)	117 (70.1%)	599 (18.7%)
Operation type	Laparoscopic	536 (45.3%)	1178 (63.4%)	37 (22.2%)	1751 (54.6%)
	Open	647 (54.7%)	680 (36.6%)	130 (77.8%)	1457 (45.4%)
Extent of surgery	Complete (C4)	345 (29.2%)	543 (29.2%)	38 (22.8%)	926 (28.9%)
	Extended (C5-7)	596 (50.4%)	912 (49.1%)	61 (36.5%)	1569 (48.9%)
	Limited (C1-3)	232 (19.6%)	385 (20.7%)	66 (39.5%)	683 (21.3%)
	Missing	10 (0.8%)	18 (1%)	2 (1.2%)	30 (0.9%)

% shown by column. SD=Standard deviation; IQR=Interquartile range.

\* Stroke or TIA

\*\* Other includes: appendix-related resections, ischaemia, volvulus, trauma and miscellaneous.

Table 2: Patient, disease and operative characteristics by overall anastomotic leak in patients for whom an anastomosis was performed

(Note - Overall anastomotic leak rate includes those with clinically or radiologically proven leak or intraperitoneal (abdominal or pelvic) fluid collection on post-operative imaging)

Variable	Overall anastomotic leak		Total (N=3041*)
	No (N=2796)	Yes (N=245)	
Patient Characteristics			
Age			
Mean [SD]	66.4 [15.9]	64.1 [16]	66.2 [15.9]
Medium [IQR]	69 [59-78]	67 [57-75]	69 [59-77]
Min - Max	16 - 99	18 - 96	16 - 99
Gender			
Male	1396 (90.6%)	144 (9.4%)	1540 (50.6%)
Female	1400 (93.3%)	101 (6.7%)	1501 (49.4%)
Body Mass Index			
Normal	1023 (92.2%)	87 (7.8%)	1110 (36.5%)
Underweight	88 (88.9%)	11 (11.1%)	99 (3.2%)
Overweight	942 (92.8%)	73 (7.2%)	1015 (33.4%)
Obese	743 (90.9%)	74 (9.1%)	817 (26.9%)
Smoking Status			
Never	1759 (92.8%)	136 (7.2%)	1895 (62.3%)
Ex-smoker	513 (91.9%)	45 (8.1%)	558 (18.4%)
Current	340 (88.5%)	44 (11.5%)	384 (12.6%)
Not known	184 (90.2%)	20 (9.8%)	204 (6.7%)
History of Ischaemic heart disease or cerebrovascular disease**			
No	2255 (92.0%)	195 (8.0%)	2450 (80.6%)
Yes	541 (91.5%)	50 (8.5%)	591 (19.4%)
History of Diabetes			
None	2363 (92.2%)	201 (7.8%)	2564 (84.3%)
Diet/Tablet controlled	344 (90.5%)	36 (9.5%)	380 (12.5%)
Insulin controlled	89 (91.8%)	8 (8.2%)	97 (3.2%)
Disease Characteristics			
Indication			
Malignant	2267 (92.8%)	175 (7.2%)	2442 (80.3%)
Crohn's Disease	312 (91.0%)	31 (9.0%)	343 (11.3%)
Other	217 (84.8%)	39 (15.2%)	256 (8.4%)
ASA grade			
Low risk	1802 (92.6%)	145 (7.4%)	1947 (64.0%)
High risk	994 (90.9%)	100 (9.1%)	1094 (36.0%)
Operative Information			
Anastomosis method			
Handsewn	1096 (92.6%)	87 (7.4%)	1183 (38.9%)
Stapled	1700 (91.5%)	158 (8.5%)	1858 (61.1%)
Surgery type			
Elective	2383 (93.1%)	176 (6.9%)	2559 (84.1%)
Emergency	413 (85.7%)	69 (14.3%)	482 (15.9%)
Operation type			
Laparoscopic	1621 (94.6%)	93 (5.4%)	1714 (56.4%)
Open	1175 (88.5%)	152 (11.5%)	1327 (43.6%)
Extent of surgery			
Complete (C4)	819 (92.2%)	69 (7.8%)	888 (29.2%)
Extended (C5-C7)	1383 (91.7%)	125 (8.3%)	1508 (49.6%)
Limited (C1-C3)	569 (92.2%)	48 (7.8%)	617 (20.3%)
Missing	25 (89.3%)	3 (10.7%)	28 (0.9%)

% shown by row. SD=Standard deviation; IQR=Interquartile range.

\*Note excludes patients who are classed as anastomosis category "none"; \*\* stroke or TIA.

Table 3: Univariate and multivariate mixed effects logistic regression analysis

Outcome (Anastomotic leak + Abscess)	Univariate analysis*				Multivariate analysis			
	Odds Ratio	95% CI	P-value	Overall p-value	Odds Ratio	95% CI	P-value	Overall p-value
Anastomosis method								
Handsewn	-	-	-	0.342	-	-	-	0.026
Stapled	1.16	(0.86, 1.57)	0.342		1.43	(1.04, 1.95)	0.026	
Patient Characteristics								
Age	0.99	(0.98, 1.00)	0.064	0.064	0.99	(0.98, 1.00)	0.037	0.037
Gender								
Male	-	-	-	0.011	-	-	-	0.066
Female	0.70	(0.53, 0.92)	0.011		0.76	(0.57, 1.02)	0.066	
Body Mass Index								
Normal	-	-	-	0.315	-	-	-	0.768
Underweight	1.46	(0.73, 2.91)	0.289		1.25	(0.61, 2.56)	0.543	
Overweight	0.93	(0.66, 1.30)	0.665		0.98	(0.69, 1.38)	0.888	
Obese	1.23	(0.87, 1.72)	0.241		1.14	(0.80, 1.64)	0.463	
Smoking Status								
Never	-	-	-	0.040	-	-	-	0.269
Ex-smoker	1.13	(0.79, 1.63)	0.504		0.99	(0.67, 1.46)	0.968	
Current smoker	1.68	(1.15, 2.43)	0.007		1.38	(0.93, 2.04)	0.106	
Not known	1.47	(0.86, 2.49)	0.158		1.41	(0.81, 2.44)	0.222	
History of Ischaemic heart disease or cerebrovascular disease								
No	-	-	-	0.766	-	-	-	0.983
Yes	1.05	(0.75, 1.47)	0.766		1.00	(0.69, 1.47)	0.983	
History of Diabetes								
None	-	-	-	0.624	-	-	-	0.375
Diet/Tablet controlled	1.21	(0.82, 1.78)	0.338		1.34	(0.89, 2.02)	0.165	
Insulin controlled	1.10	(0.51, 2.35)	0.811		1.16	(0.53, 2.55)	0.717	
Disease Characteristics								
Indication								
Malignant	-	-	-	<0.001	-	-	-	0.095
Crohns disease	1.27	(0.83, 1.93)	0.270		1.29	(0.71, 2.34)	0.398	
Other	2.39	(1.62, 3.54)	<0.001		1.73	(1.05, 2.85)	0.031	
ASA Grade								
Low risk	-	-	-	0.068	-	-	-	0.197
High risk	1.30	(0.98, 1.72)	0.068		1.24	(0.89, 1.72)	0.197	
Operative Information								
Surgery type								
Elective	-	-	-	<0.001	-	-	-	0.101
Emergency	2.33	(1.70, 3.19)	<0.001		1.40	(0.94, 2.09)	0.101	
Operation type								
Laparoscopy	-	-	-	<0.001	-	-	-	<0.001
Open	2.32	(1.74, 3.08)	<0.001		2.09	(1.53, 2.87)	<0.001	

<b>Extent of surgery</b>								
Complete (C4)	-	-	-		-	-	-	
Extended (C5-C7)	1.07	(0.77, 1.48)	0.688	0.869	1.10	(0.79, 1.53)	0.568	0.139
Limited (C1-C3)	0.98	(0.66, 1.47)	0.925		0.70	(0.44, 1.11)	0.132	

\* Univariate analysis included centre as a random effect to taken into account variation across centres.

Table 4: The impact of overall anastomotic leak (and the group with only a 'proven' leak) on clinical outcomes

Group	n	30-day death rate (n; %)	Length of stay (days; median (IQR))
Full cohort	3208	103 (3.2%)	7 (5-11)
No anastomosis made	167	30 (18.0%)	11 (7-20)
In those undergoing anastomosis:	3041	73 (2.4%)	7 (5-10)
No leak or collection evident	2796	49 (1.8%)	7 (5-10)
Anastomotic leak and/or collection*	245	24 (9.8%)	18 (10-27)
Proven anastomotic leak only	150	17 (11.3%)	21 (13-30)

\*the primary outcome of this study. IQR=Interquartile range.

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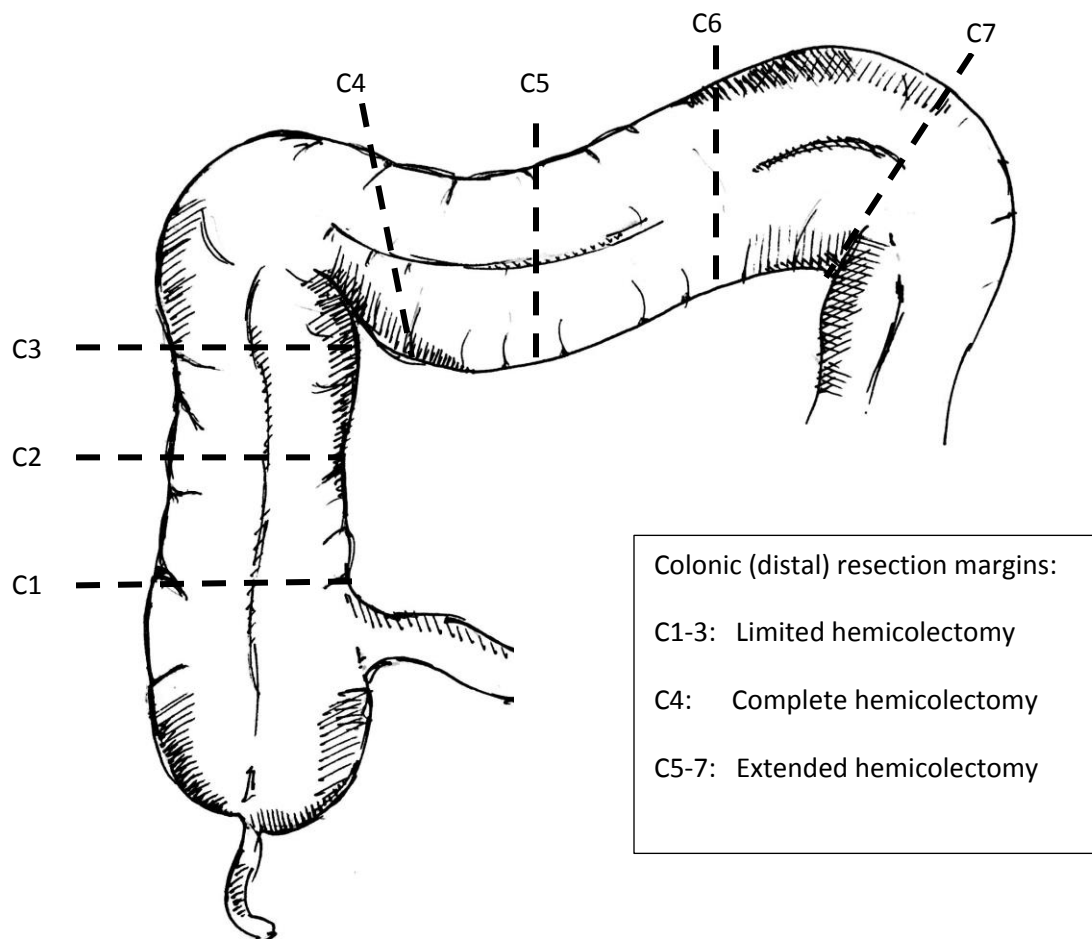
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Figure 1: Classification of anastomotic leak

Grade A - Anastomotic leakage requiring no active intervention (diagnosed radiologically)
Grade B - Anastomotic leakage requiring active radiological intervention but manageable without surgical re-intervention
Grade C - Anastomotic leakage requiring surgical re-intervention

*NB - Highest score during follow up; e.g. Grade C if percutaneous drainage is followed by laparotomy*

Figure 2: Extent of resection – distal resection (colonic) margins as allocated on post-operative CRF





**Total centres**

- None
- 1-4
- 5-10
- 11-20
- >21

The map displays the following data for European countries:

Country	Total Centres
Iceland	1
Finland	4
Sweden	3
Norway	8
Denmark	1
Poland	5
Czechia	1
Slovakia	4
Hungary	1
Romania	5
Bulgaria	1
Greece	2
Turkey	5
Ukraine	1
Belarus	1
Latvia	1
Lithuania	1
Malta	1
Cyprus	1
Portugal	7
Spain	59
France	6
Germany	7
Austria	5
Italy	26
Switzerland	3
Netherlands	9
Belgium	20
United Kingdom	56
Republic of Ireland	3
Albania	1
Slovenia	7
Croatia	1
Serbia	1
Bosnia and Herzegovina	1
Montenegro	1
Moldova	1
Russia	5
Georgia	4
Armenia	1
Azerbaijan	1
Yemen	6